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10/001,267	10/31/2001	Lakshmi Rambhatla	093/004P	1874

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EXAMINER

TON, THAIAN N

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

94-

Office Action Summary**Application No.**

10/001,267

Applicant(s)

RAMBHATLA ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/21/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's Amendment, filed 6/9/2004, has been entered. Claims 13, 19, 20, 26-28 have been amended. Claims 29-40 have been added. Claims 13-40 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed on 6/9/04 has been considered and made of record.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 13-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 9-13 17-19 of copending Application No. 10/087,142 is maintained for reasons of record. Applicants acknowledge the rejection and state that upon indication of patentable

subject matter, Applicants undertake to file a terminal disclaimer or to take other appropriate action to obviate double patenting. See p. 7 of Applicants' Response. The rejection is maintained because Applicants have not shown how the claims are patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 13-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,458,589 B1 [Published October 1, 2002]. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method claims for producing differentiated primate pluripotent stem cells are made obvious by the cell populations (the hES cells and differentiated cells) because the cell populations of the '589 patent have the same characteristics as the cells produced by the methods of the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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The prior rejection of claim 28 is withdrawn in view of Applicants' arguments.

A new rejection appears below.

Claims 13-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for producing hepatocytes from primate pluripotent stem [pPS] cells by 1) obtaining a culture of pPS cells, 2) initiating differentiation of the pPS cells and 3) culturing the cells from step 2) in a medium containing a histone deacetylase inhibitor, does not reasonably provide enablement for the breadth of the claims for producing hepatocytes from pPS cells by optionally initiating differentiation of the pPS cells prior to culturing them in a medium containing a histone deacetylase inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification teaches that histone deacetylase inhibitors, like butyrate and trichostatin A have been implicated in the differentiation of a wide variety of cell types, and that it would be logical to expect that such differentiation would produce a large heterogenous population of cells, but the instant invention shows that a homogenous population of hepatocytes is produced. See p. 6, lines 33-38. The specification further points to the state art to show that histone deacetylase

inhibitors have been found to initiate differentiation in many cell types [e.g., squamous carcinoma cell lines, human neuroblastoma cells, seminal vesicle epithelial cells, human keratinocytes, etc.]. See p. 8, lines 3-15.

The working examples in the specification teach 1) the production of embryoid body cells, which are then cultured in medium containing n-butyrate to form hepatocytes or 2) the induction of differentiation of undifferentiated ES cells with SR medium, and then the subsequent addition of n-butyrate [referred to as direct differentiation in the specification]. See Example 1 and 5. The formation of embryoid bodies from a donor pPS culture results in cells that endoderm, mesoderm and ectoderm [see p. 16, lines 1-5, for example]. Thus, the embryoid body cells described in the instant specification are cells that have been differentiated. Further, the specification teaches that when undifferentiated pPS cells are cultured in SR medium in the absence of n-butyrate, they differentiate into cells with different morphologies. See p. 42, lines 17-20. The working examples provided by the instant specification specifically initiate differentiation prior to the culturing of the resulting cells with a histone deacetylase inhibitor. The working examples fail to teach a scenario wherein undifferentiated ES cells are cultured directly with a histone deacetylase inhibitor to produce cells of those instantly claimed. This is because the state of the art teaches that inhibition of histone deacetylase activity inhibits differentiation.

For example, Lee *et al.* [Genesis, 38:32-38 (2004)] teach that histone deacetylase activity is required for ES cell differentiation. Particularly, that mouse ES cells treated with trichostatin A [specifically recited in claim 18] blocked the initial wave of histone deacetylation that is normally observed upon the induction of ES cell differentiation and drastically inhibits ES cell differentiation, shown by inhibition of embryoid body formation. See p. 34, 1st ¶ and Figure 3. Lee teach that withdrawal of trichostatin A resulted in the initiation of histone deacetylation and the subsequent formation of embryoid bodies. See p. 36, 1st column and Figure 3b. Lee conclude that, “[H]istone deacetylases and acetylases transmit differentiation signals to initiate appropriate epigenetic modifications, such as erasure of preexisting chromatin structure and establishment of new histone modification patterns during *in vitro* differentiation of ES cells.” See p. 37, 2nd ¶, last sentence.

Accordingly, the instant claims are not enabled because in view of the state of the art, which teaches that histone deacetylase activity is required for ES cell differentiation, and the teachings of the specification which show that initiation of differentiation – either through formation of embryoid bodies, or by specific culture conditions – is a critical and required step to practice the claimed invention. Thus, in view of the state of the art and the working examples provided by the instant specification, it would have required undue experimentation for one of ordinary skill in the art to practice the claimed methods by optionally differentiating the pPS cells

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and culturing the cells in a medium containing a histone deacetylase inhibitor to produce hepatocytes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejections of claims 13 and 28 are withdrawn.

Claim 13, as amended, is unclear because the claim recites “the cells” in part (c) of the claim. It unclear which cells (the undifferentiated pPS cells of part (a) or the optionally differentiated cells in part (b)) are being cultured. Appropriate correction is required. Claims 14-25, 29 and 30 depend from claim 13.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claim 28 is withdrawn in view of Applicants’ arguments and/or amendment(s) to the claim.

The prior rejection of claim 27, and newly added claims 31-33 is *maintained* under 35 U.S.C. 102(b) as being anticipated by Kaneko *et al.* [cited in the prior

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Office action] for reasons of record. Applicants do not present any arguments with regard to the prior rejection. Note that claim 27, as amended, does not overcome the prior rejection because the cells differentiated “from an established culture of primate pluripotent stem cells” are not distinguished from the hepatocytes, as taught by Kaneko.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt

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